

## Chapter 307

# Superiority by a Margin Tests for Two Total Variances in a 2×2M Replicated Cross-Over Design

## Introduction

This procedure calculates power and sample size of *superiority by a margin* tests of total variabilities (between + within) from a 2×2M replicated cross-over design. This routine deals with the case in which the statistical hypotheses are expressed in terms of the ratio of the total variances.

This design is used to compare two treatments which are administered to subjects in different orders. The design has two treatment sequences. Here,  $M$  is the number of times a particular treatment is received by a subject.

For example, if  $M = 2$ , the design is a 2×4 replicated cross-over. The two sequences might be

sequence 1: C T C T

sequence 2: T C T C

It is assumed that either there is no carry-over from one measurement to the next, or there is an ample washout period between measurements.

## Technical Details

This procedure uses the formulation given in Chow, Shao, Wang, and Lokhnygina (2018), pages 227 - 230.

Suppose  $x_{ijkl}$  is the response in the  $i$ th sequence ( $i = 1, 2$ ),  $j$ th subject ( $j = 1, \dots, N$ ),  $k$ th treatment ( $k = T, C$ ), and  $l$ th replicate ( $l = 1, \dots, M$ ). The mixed effect model analyzed in this procedure is

$$x_{ijkl} = \mu_k + \gamma_{ikl} + S_{ijk} + e_{ijkl}$$

where  $\mu_k$  is the  $k$ th treatment effect,  $\gamma_{ikl}$  is the fixed effect of the  $l$ th replicate on treatment  $k$  in the  $i$ th sequence,  $S_{ij1}$  and  $S_{ij2}$  are random effects of the  $j$ th subject, and  $e_{ijkl}$  is the within-subject error term which is normally distributed with mean 0 and variance  $V_k = \sigma_{Wk}^2$ .

Unbiased estimators of these variances are found after applying an orthogonal transformation matrix  $P$  to the  $x$ 's as follows

$$z_{ijk} = P'x_{ijk}$$

where  $P$  is an  $m \times m$  matrix such that  $P'P$  is diagonal and  $\text{var}(z_{ijkl}) = \sigma_{Wk}^2$ .

## Superiority by a Margin Tests for Two Total Variances in a 2x2M Replicated Cross-Over Design

Let  $N_s = N_1 + N_2 - 2$ . In a 2x4 cross-over design the z's become

$$z_{ijk1} = \frac{x_{ijk1} + x_{ijk2}}{2} = \bar{x}_{ijk}.$$

and

$$z_{ijk2} = \frac{x_{ijk1} - x_{ijk2}}{\sqrt{2}} = \bar{x}_{ijk}.$$

In this case, the within-subject variances are estimated as

$$s_{WT}^2 = \frac{1}{N_s(M-1)} \sum_{i=1}^2 \sum_{j=1}^{N_i} \sum_{l=1}^M (z_{ijTl} - \bar{z}_{i.Tl})^2$$

and

$$s_{WC}^2 = \frac{1}{N_s(M-1)} \sum_{i=1}^2 \sum_{j=1}^{N_i} \sum_{l=1}^M (z_{ijCl} - \bar{z}_{i.Cl})^2$$

Similarly, the between-subject variances are estimated as

$$s_{BT}^2 = \frac{1}{N_s} \sum_{i=1}^2 \sum_{j=1}^{N_i} (\bar{x}_{ijT.} - \bar{x}_{i.T.})^2$$

and

$$s_{BC}^2 = \frac{1}{N_s} \sum_{i=1}^2 \sum_{j=1}^{N_i} (\bar{x}_{ijC.} - \bar{x}_{i.C.})^2$$

where

$$\bar{x}_{i.k.} = \frac{1}{N_i} \sum_{j=1}^{N_i} \bar{x}_{ijk.}$$

Now, since  $E(s_{BK}^2) = \sigma_{BK}^2 + \sigma_{WK}^2/M$ , estimators for the total variance are given by

$$\hat{\sigma}_{TK}^2 = s_{BK}^2 + \frac{(M-1)}{M} \hat{\sigma}_{WK}^2$$

## Superiority by a Margin Tests for Two Total Variances in a 2x2M Replicated Cross-Over Design

The sample between-subject covariance is calculated using

$$s_{BTC}^2 = \frac{1}{N_s} \sum_{i=1}^2 \sum_{j=1}^{N_i} (\bar{x}_{ijT.} - \bar{x}_{i.T.})(\bar{x}_{ijC.} - \bar{x}_{i.C.})$$

Using this value, the sample between-subject correlation is easily calculated.

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### Testing Variance Superiority

The following statistical hypotheses are used to test for total variance non-inferiority.

$$H_0: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} \geq R0 \quad \text{versus} \quad H_1: \frac{\sigma_{TT}^2}{\sigma_{TC}^2} < R0,$$

where  $R0$  is the superiority limit.

Let  $\eta = \sigma_{TT}^2 - R0\sigma_{TC}^2$  be the parameter of interest. The test statistic is  $\hat{\eta} = \hat{\sigma}_{TT}^2 - R0\hat{\sigma}_{TC}^2$ .

### Superiority by a Margin Test

For the superiority test, compute the limit  $\hat{\eta}_U$  using  $\hat{\eta}_U = \hat{\eta} + \sqrt{\Delta_U}$

Reject the null hypothesis if  $\hat{\eta}_U < 0$ .

The  $\Delta$  is given by

$$\begin{aligned} \Delta_U = & h(1 - \alpha, N_s - 1)\lambda_1^2 + h(\alpha, N_s - 1)\lambda_2^2 + h(1 - \alpha, N_s(M - 1)) \left[ \frac{(M - 1)\hat{\sigma}_{WT}^2}{M} \right]^2 \\ & + h(\alpha, N_s(M - 1)) \left[ \frac{(M - 1)\hat{\sigma}_{WC}^2}{M} \right]^2 \end{aligned}$$

where

$$h(A, B) = \left( 1 - \frac{B}{\chi_{A,B}^2} \right)^2$$

$$\lambda_i^2 = \left( \frac{s_{BT}^2 - s_{BC}^2 \pm \sqrt{(s_{BT}^2 + s_{BC}^2)^2 - 4(R0)s_{BTC}^4}}{2} \right) \text{ for } i = 1, 2$$

and  $\chi_{A,B}^2$  is the upper quantile of the chi-square distribution with  $B$  degrees of freedom.

## Power

### Superiority by a Margin Test

The power of the superiority test is given by

$$\text{Power} = \Phi \left( z_{\alpha} - \frac{(R_1 - R_0)\sigma_{TC}^2}{\sqrt{\sigma^{*2}/N_s}} \right)$$

where

$$R_1 = \frac{\sigma_{TT}^2}{\sigma_{TC}^2}$$

$$\sigma_{TT}^2 = R_1 \sigma_{TC}^2$$

$$\sigma^{*2} = 2 \left[ \left( \sigma_{BT}^2 + \frac{\sigma_{WT}^2}{M} \right)^2 + R_0^2 \left( \sigma_{BC}^2 + \frac{\sigma_{WC}^2}{M} \right)^2 + \frac{(M-1)\sigma_{WT}^4}{M^2} + \frac{(M-1)R_0^2\sigma_{WC}^4}{M^2} - 2R_0\sigma_{BT}^2\sigma_{BC}^2\rho^2 \right]$$

A simple binary search algorithm can be applied to the power function to obtain an estimate of the necessary sample size.

# Example 1 – Finding Sample Size

A company has developed a generic drug for treating rheumatism and wants to show that it is superior to the standard drug in terms of the total variability. A 2 x 4 cross-over design will be used to test the superiority.

Company researchers set the superior limit to 0.8, the significance level to 0.05, the power to 0.90, M to 2, and the actual variance ratio values between 0.4 and 0.7. They also set  $\sigma^2_{TC} = 0.8$ ,  $\sigma^2_{WT} = 0.2$ ,  $\sigma^2_{WC} = 0.3$ , and  $\rho = 0.7$ . They want to investigate the range of required sample size values assuming that the two sequence sample sizes are equal.

## Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

|   |                        |
|---|------------------------|
| Design Tab                                    |                        |
| Solve For .....                               | <b>Sample Size</b>     |
| Power.....                                    | <b>0.90</b>            |
| Alpha.....                                    | <b>0.05</b>            |
| Sequence Allocation .....                     | <b>Equal (N1 = N2)</b> |
| M (Number of Replicates) .....                | <b>2</b>               |
| R0 (Superiority Variance Ratio) .....         | <b>0.8</b>             |
| R1 (Actual Variance Ratio) .....              | <b>0.4 0.5 0.6 0.7</b> |
| $\sigma^2_{TC}$ (Control Variance).....       | <b>0.8</b>             |
| $\sigma^2_{WT}$ (Treatment Variance) .....    | <b>0.2</b>             |
| $\sigma^2_{WC}$ (Control Variance).....       | <b>0.3</b>             |
| $\rho$ (Treatment, Control Correlation) ..... | <b>0.7</b>             |

## Superiority by a Margin Tests for Two Total Variances in a 2x2M Replicated Cross-Over Design

## Output

Click the Calculate button to perform the calculations and generate the following output.

## Numeric Reports

## Numeric Results

Solve For: [Sample Size](#)

Hypotheses:  $H_0: \sigma^2_{TT}/\sigma^2_{TC} \geq R_0$  vs.  $H_1: \sigma^2_{TT}/\sigma^2_{TC} < R_0$

| Power  |        | Sequence Sample Size |     |     | Number of Replicates | Total Variance    |              |                         | Within-Subject Variance   |                         | Between-Subject (Treatment, Control) Correlation |       |
|--------|--------|----------------------|-----|-----|----------------------|-------------------|--------------|-------------------------|---------------------------|-------------------------|--|-------|
|        |        |                      |     |     |                      | Ratio             |              | Control $\sigma^2_{TC}$ | Treatment $\sigma^2_{WT}$ | Control $\sigma^2_{WC}$ | $\rho$   | Alpha |
|        |        |                      |     |     |                      | Superiority $R_0$ | Actual $R_1$ |                         |                           |                         |  |       |
| Target | Actual | N1                   | N2  | N   | M                    |                   |              |                         |                           |                         |  |       |
| 0.9    | 0.9024 | 26                   | 26  | 52  | 2                    | 0.8               | 0.4          | 0.8                     | 0.2                       | 0.3                     | 0.7  | 0.05  |
| 0.9    | 0.9025 | 47                   | 47  | 94  | 2                    | 0.8               | 0.5          | 0.8                     | 0.2                       | 0.3                     | 0.7  | 0.05  |
| 0.9    | 0.9018 | 112                  | 112 | 224 | 2                    | 0.8               | 0.6          | 0.8                     | 0.2                       | 0.3                     | 0.7  | 0.05  |
| 0.9    | 0.9001 | 490                  | 490 | 980 | 2                    | 0.8               | 0.7          | 0.8                     | 0.2                       | 0.3                     | 0.7  | 0.05  |

|                 |  |
|-----------------|--|
| Target Power    | The desired power value entered in the procedure. Power is the probability of rejecting a false null hypothesis.                           |
| Actual Power    | The actual power achieved. Because N1 and N2 are discrete, this value is usually slightly larger than the target power.                    |
| N1              | The number of subjects in sequence 1.  |
| N2              | The number of subjects in sequence 2.  |
| N               | The total number of subjects. $N = N_1 + N_2$ .  |
| M               | The number of replicates. That is, it is the number of times a treatment measurement is repeated on a subject.                             |
| R0              | The superiority limit for the total variance ratio.  |
| R1              | The value of the total variance ratio at which the power is calculated.  |
| $\sigma^2_{TC}$ | The total variance of measurements in the control group. Note that $\sigma^2_{TC} = \sigma^2_{BC} + \sigma^2_{WC}$ .                       |
| $\sigma^2_{WT}$ | The within-subject variance of measurements in the treatment group.  |
| $\sigma^2_{WC}$ | The within-subject variance of measurements in the control group.  |
| $\rho$          | The between-subject correlation of the average subject treatment-group measurements versus the average subject control-group measurements. |
| Alpha           | The probability of rejecting a true null hypothesis.   |

## Summary Statements

A 2x2M replicated cross-over design will be used to test whether the total variance of the treatment ( $\sigma^2_{TT}$ ) is superior to the total variance of the control ( $\sigma^2_{TC}$ ) by a margin by testing the total variance ratio ( $\sigma^2_{TT} / \sigma^2_{TC}$ ) against the superiority ratio 0.8 ( $H_0: \sigma^2_{TT} / \sigma^2_{TC} \geq 0.8$  versus  $H_1: \sigma^2_{TT} / \sigma^2_{TC} < 0.8$ ). With 2 replicate pairs, each subject will be measured 4 times. For those in the Sequence 1 group, the first treatment will be C, and the sequence is [C T C T]. For those in the Sequence 2 group, the first treatment will be T, and the sequence is [T C T C]. The comparison will be made using a one-sided, variance-difference test (treatment minus control) as described in Chow, Shao, Wang, and Lohhnygina (2018), with a Type I error rate ( $\alpha$ ) of 0.05. For the control group, the total variance ( $\sigma^2_{TC}$ ) is assumed to be 0.8, and the within-subject variance is assumed to be 0.3. The within-subject variance of the treatment group is assumed to be 0.2. The between-subject correlation between the average treatment measurement per subject and the average control measurement per subject is assumed to be 0.7. To detect a total variance ratio ( $\sigma^2_{TT} / \sigma^2_{TC}$ ) of 0.4 with 90% power, the number of subjects needed will be 26 in Group/Sequence 1, and 26 in Group/Sequence 2.

## Superiority by a Margin Tests for Two Total Variances in a 2x2M Replicated Cross-Over Design

## Dropout-Inflated Sample Size

| Dropout Rate | Sample Size |     |     | Dropout-Inflated Enrollment Sample Size |     |      | Expected Number of Dropouts |     |     |
|--------------|-------------|-----|-----|---|-----|------|-----------------------------|-----|-----|
|              | N1          | N2  | N   | N1'                                     | N2' | N'   | D1                          | D2  | D   |
| 20%          | 26          | 26  | 52  | 33                                      | 33  | 66   | 7                           | 7   | 14  |
| 20%          | 47          | 47  | 94  | 59                                      | 59  | 118  | 12                          | 12  | 24  |
| 20%          | 112         | 112 | 224 | 140                                     | 140 | 280  | 28                          | 28  | 56  |
| 20%          | 490         | 490 | 980 | 613                                     | 613 | 1226 | 123                         | 123 | 246 |

|                  |   |
|------------------|---|
| Dropout Rate     | The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.  |
| N1, N2, and N    | The evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.  |
| N1', N2', and N' | The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas $N1' = N1 / (1 - DR)$ and $N2' = N2 / (1 - DR)$ , with N1' and N2' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.) |
| D1, D2, and D    | The expected number of dropouts. $D1 = N1' - N1$ , $D2 = N2' - N2$ , and $D = D1 + D2$ .  |

## Dropout Summary Statements

Anticipating a 20% dropout rate, 33 subjects should be enrolled in Group 1, and 33 in Group 2, to obtain final group sample sizes of 26 and 26, respectively.

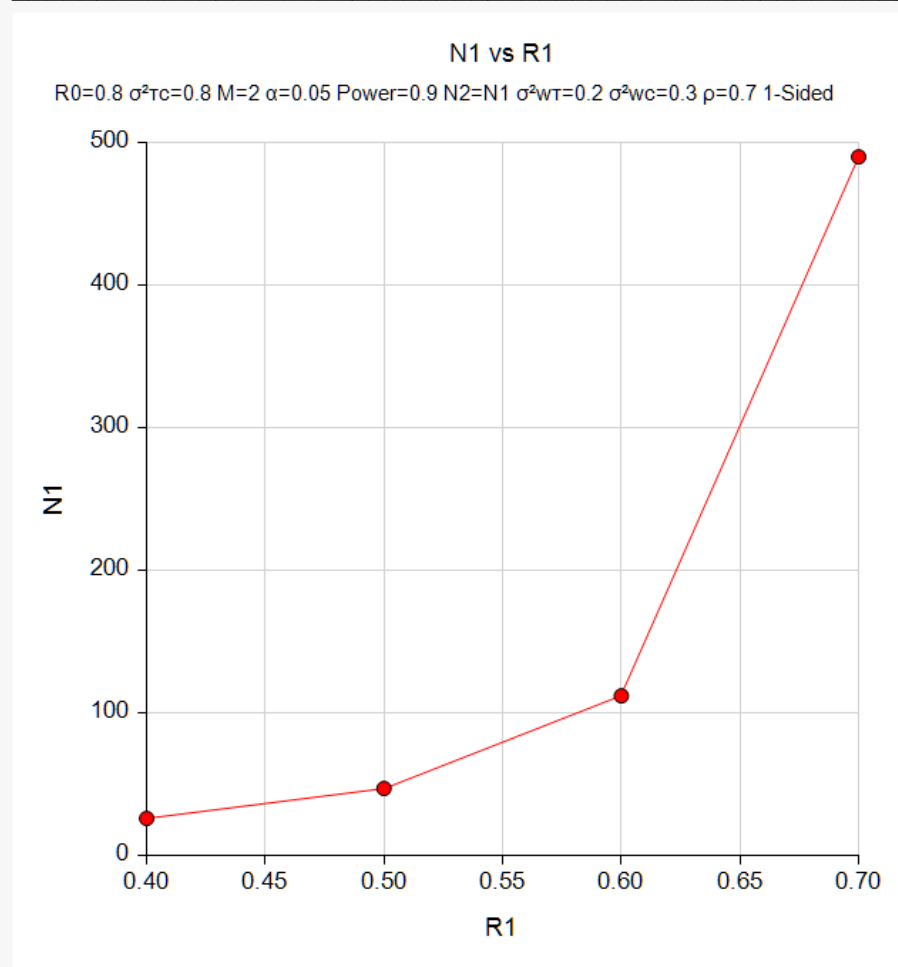
## References

- Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
- Chow, S.C., and Liu, J.P. 2014. Design and Analysis of Clinical Trials, Third Edition. John Wiley & Sons. Hoboken, New Jersey.

This report gives the sample sizes for the indicated scenarios.

## Plots Section

### Plots



This plot shows the relationship between sample size and R1.



## Example 2 – Validation using Hand Calculations

We could not find an example in the literature, so we will present hand calculations to validate this procedure.

Set  $N_1 = 47$ ,  $R_0 = 0.8$ , significance level = 0.05,  $M = 2$ , and  $R_1 = 0.5$ . Also,  $\sigma^2_{TC} = 0.8$ ,  $\sigma^2_{WT} = 0.2$ ,  $\sigma^2_{WC} = 0.3$ , and  $\rho = 0.7$ . Compute the power for the superiority test.

The calculations proceed as follows:

$$\sigma^2_{TT} = R_1(\sigma^2_{TC}) = 0.5(0.8) = 0.4$$

$$\sigma^2_{BT} = \sigma^2_{TT} - \sigma^2_{WT} = 0.4 - 0.2 = 0.2$$

$$\sigma^2_{BC} = \sigma^2_{TC} - \sigma^2_{WC} = 0.8 - 0.3 = 0.5$$

$$\sigma^{*2} = 2 \left[ \left( \sigma^2_{BT} + \frac{\sigma^2_{WT}}{M} \right)^2 + R_0^2 \left( \sigma^2_{BC} + \frac{\sigma^2_{WC}}{M} \right)^2 + \frac{(M-1)\sigma^4_{WT}}{M^2} + \frac{(M-1)R_0^2\sigma^4_{WC}}{M^2} - 2R_0\sigma^2_{BT}\sigma^2_{BC}\rho^2 \right]$$

$$\sigma^{*2} = 2 \left[ \left( 0.2 + \frac{0.2}{2} \right)^2 + 0.64 \left( 0.5 + \frac{0.3}{2} \right)^2 + \frac{0.04}{4} + \frac{0.64(0.09)}{4} - 2(0.8)(0.2)(0.5)(0.49) \right]$$

$$\sigma^{*2} = 2[0.09 + 0.2704 + 0.01 + 0.0144 - 0.0784] = 0.6128$$

$$\text{Power} = \Phi \left( z_\alpha - \frac{(R_1 - R_0)\sigma^2_{TC}}{\sqrt{\sigma^{*2}/N_s}} \right)$$

$$\text{Power} = \Phi \left( -1.6448536 - \frac{(0.5 - 0.8)0.8}{\sqrt{0.6128/92}} \right)$$

$$\text{Power} = \Phi(-1.6448536 + 2.94066652)$$

$$\text{Power} = \Phi(1.29581292) = 0.90248003$$

## Superiority by a Margin Tests for Two Total Variances in a 2x2M Replicated Cross-Over Design

## Setup

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### Design Tab

Solve For ..... **Power**  
 Alpha..... **0.05**  
 Sequence Allocation ..... **Equal (N1 = N2)**  
 Sample Size Per Sequence ..... **47**  
 M (Number of Replicates) ..... **2**  
 R0 (Superiority Variance Ratio) ..... **0.8**  
 R1 (Actual Variance Ratio) ..... **0.5**  
 $\sigma^2_{TC}$  (Control Variance)..... **0.8**  
 $\sigma^2_{WT}$  (Treatment Variance) ..... **0.2**  
 $\sigma^2_{WC}$  (Control Variance)..... **0.3**  
 $\rho$  (Treatment, Control Correlation) ..... **0.7**

## Output

Click the Calculate button to perform the calculations and generate the following output.

### Numeric Results

Solve For: **Power**

Hypotheses:  $H_0: \sigma^2_{TT}/\sigma^2_{TC} \geq R_0$  vs.  $H_1: \sigma^2_{TT}/\sigma^2_{TC} < R_0$

| Power  | Sequence Sample Size |    |    | Number of Replicates<br>M | Total Variance    |              |                            | Within-Subject Variance      |                            | Between-Subject<br>(Treatment, Control)<br>Correlation<br>$\rho$ | Alpha |
|--------|----------------------|----|----|---------------------------|-------------------|--------------|----------------------------|------------------------------|----------------------------|--|-------|
|        | N1                   | N2 | N  |                           | Ratio             |              | Control<br>$\sigma^2_{tc}$ | Treatment<br>$\sigma^2_{wt}$ | Control<br>$\sigma^2_{wc}$ |  |       |
|        |                      |    |    |                           | Superiority<br>R0 | Actual<br>R1 |                            |                              |                            |  |       |
|        |                      |    |    |                           |                   |              |                            |                              |                            |  |       |
| 0.9025 | 47                   | 47 | 94 | 2                         | 0.8               | 0.5          | 0.8                        | 0.2                          | 0.3                        | 0.7  | 0.05  |

The power matches the result calculated by hand above.